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Cytomegalovirus Retinitis and Low-Grade Non-Hodgkin's Lymphoma: Case Report and Review of the Literature

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Patients with non-Hodgkin's lymphoma may develop retinal or choroidal lesions during the course of their disease. New immunosuppressive therapies currently used in reticuloendothelial malignancies have increased the incidence of opportunistic infections in this patient population. The differentiation of lymphomatous infiltration from opportunistic infection as a cause of chorioretinal infiltrates is critical, as the treatments are fundamentally different. We report a case of a patient with non-Hodgkin's lymphoma who developed a chorioretinal infiltrate that was initially thought to represent progressive disease. The patient received radiation treatment appropriate for intraocular lymphoma. The lesion progressed further and after reevaluation a diagnosis of cytomegalovirus retinitis was made and therapy initiated. Review of the literature for intraocular lymphoma and cytomegalovirus retinitis is provided and diagnostic strategies are described. We recommend analysis of intraocular fluid when there is difficulty in clinically differentiating intraocular lymphoma from opportunistic infection. Am. J. Hematol. 57:228–232, 1998. © 1998 Wiley-Liss, Inc.

Key words: cytomegalovirus retinitis; non-Hodgkin's lymphoma; opportunistic infection

INTRODUCTION

Non-Hodgkin's lymphoma is a reticuloendothelial malignancy characterized by a malignant proliferation of lymphocytes, usually of the B-cell lineage. The chemotherapeutic regimens used to treat this disease, particularly some of the newer purine analogs, may exacerbate the underlying defects in cellular immunity and increase the predisposition of these patients to opportunistic infections. The current literature contains several case reports describing opportunistic infections in lymphoma patients treated with chemotherapy. We describe a case of cytomegalovirus retinitis in a patient who received treatment with newer immunosuppressive therapies for low-grade non-Hodgkin's lymphoma.

CASE REPORT

A 47-year-old previously healthy man presented in May 1991 with bilateral axillary masses and a recent flu-like illness. Physical and radiologic examination revealed diffuse cervical, supraclavicular, bilateral axillary, and periaortic adenopathy and hepatomegaly. Laboratory blood results were normal including serology for HIV. Following a supraclavicular lymph node biopsy in June 1991, the patient was diagnosed with Stage IV (on the basis of a positive bone marrow biopsy and an enlarged liver) low-grade lymphoma, follicular, predominantly small cleaved cell type.

After disease progression in June 1992, he underwent treatment with 12 courses of CVP (cyclophosphamide, vincristine, and prednisone) chemotherapy. Response to the chemotherapy was incomplete and followed by progression of the disease 12 weeks post-chemotherapy.

The patient was entered in a phase II clinical trial of

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CAMPATH® 1H monoclonal antibody and received 47 CAMPATH® infusions (25 mg each) between January 1994 and May 1994 and obtained a partial objective response, but still had multiple areas of disease. He was started on fludarabine in June 1994 because of symptomatic bulky disease. The patient responded initially but after four cylces of fludarabine, the response plateaued. The patient began to develop diffuse cutaneous tumour nodules requiring several courses of localized radiation therapy with palliative intent. He continued to have moderate to bulky disease in his abdomen and in peripheral sites necessitating treatment with chlorambucil and prednisone.

The patient had been followed by the ophthalmology service since August 1993 for a clinical diagnosis of asymptomatic lymphomatous involvement of the conjunctivae bilaterally. In December 1994 the patient's ophthalmologist noted a perivascular patch of retinochoroidal yellow-white discoloration with associated retinal haemorrhages inferior to the right optic disc measuring 3 to 4 disc diameters in size (Fig. 1a,b) A palpable mass was also found in the region of the right lacrimal gland. The best corrected visual acuity was 20/40 OD and 20/30 OS. A diagnosis of lymphomatous retinal infiltrate OD and lymphomatous involvement of the right lacrimal gland was made. The patient underwent 2,000 Rads of Cobalt 60 gamma irradiation in a rectangular field covering the right globe and orbit. Two weeks later, the mass in the right lacrimal gland had completely regressed but the patient's retinal disease had progressed in the right eye. By February 1995, the retina inferior to the right optic nerve had detached, and there was now associated vitreous haemorrhage and a more peripheral area of retinal necrosis (Fig. 1c). Results of a consultation with a retina specialist suggested that the patient's right eye had evidence of active cytomegalovirus retinitis complicated by retinal detachment.

The patient underwent 2 weeks of induction with systemic gancyclovir in conjunction with three intravitreal injections of 400 mcg/0.1 cc gancyclovir. The intravenous gancyclovir was complicated by neutropenia necessitating the use of adjunctive G-CSF. The patient was then taken to the operating room for a parsplana vitrectomy, membrane peel, endodrainage of subretinal fluid, air-fluid exchange, and silicone oil injection. Analysis of vitreous fluid obtained intraoperatively revealed inflammatory cells only and no lymphoma cells on cytology, negative bacterial and fungal cultures, and negative Zeil Neilson stain. Cytomegalovirus was isolated from the vitreous fluid after 4 weeks of culture in human fibroblast tissue. PCR on vitreous fluid was also performed, and was positive for cytomegalovirus. Serum testing in February 1995 revealed the presence of CMV IgG antibodies.

In March 1995, the systemic disease appeared to be undergoing transformation to a more aggressive histology. CHOP (cyclophosphamide, adriamycin, vincristine, and prednisone) chemotherapy was begun with good response. Despite retinal rettachment, his CMV retinitis progressed and was unresponsive to IV gancyclovir. The visual acuity OD dropped to no light perception and the patient developed a blind and painful right eye. The pain was not relieved with oral analgesics or retrobulbar Kenalog injections, and the patient eventually required enucleation of the right globe in July 1995. Ocular pathology revealed features consistent with the diagnosis of CMV retinitis.

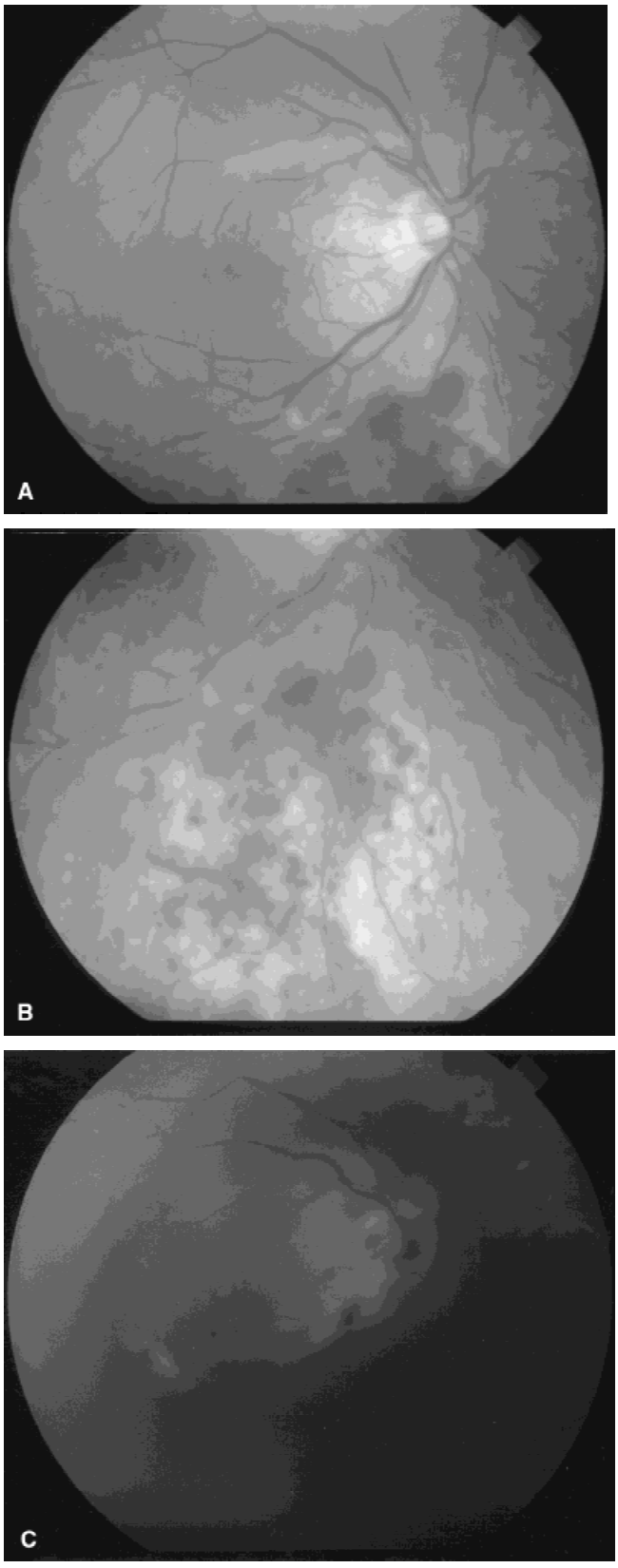
In September 1995, the patient developed CMV retinitis in the left eye. Foscarnet induction resulted in severe pancytopenia and, subsequently, admission to the hospital. While in the hospital, a previously diagnosed abdominal aortic aneurysm was found to be enlarging on repeat CT scan and the patient was taken to the operating room for resection of the aortic aneurysm. Culture of the aortic tissue was positive for mycobacterium tuberculosis. The patient expired shortly after surgery.

DISCUSSION

The incidence of ocular infiltration in patients with a previously diagnosed systemic non-Hodgkin's lymphoma is likely less than 1% [1,2] (Gospodarowicz and Sutcliffe, personal communication). Intraocular lymphoma is usually associated with isolated CNS lymphoma (50–80%) and less commonly with isolated visceral lymphoma (5–29%) or both CNS and visceral disease (6–10%). The ocular lymphoma associated with CNS disease typically involves the retina and vitreous, while that associated with systemic/visceral disease typically involves the uvea. Bilaterality of intraocular lymphoma is not uncommon [3–5]. Intraocular lymphoma can manifest as a chronic posterior uveitis involving the vitreous (vitreous cells in strands, sheets, or clumps), retinitis (perivascular yellowish-white retinal infiltrates with or without haemorrhages), retinal vasculitis (sheathing of arteries and veins) [6], or choroiditis (solitary or multiple creamy yellow or greyish subretinal masses) [7,8]. The clinical ophthalmologic findings are often not specific and in difficult cases tissue analysis may be necessary.

Intraocular lymphoma can easily be confused with many ocular infectious and inflammatory conditions [7,8]. The differential includes infections such as: cytomegalovirus, toxoplasmosis, syphilis, candida, pneumocystis, varicella zoster, herpes simplex infections [9], and inflammatory conditions such as sarcoidosis, acute multifocal placoid pigment epitheliopathy, and multiple evanescent white dot syndrome [8].

CMV retinitis, in particular, can resemble the retinal form of intraocular lymphoma. The typical appearance of



CMV retinitis is that of a focal discrete perivascular retinal whitening or yellowing with or without haemorrhage, which progresses by centrifugal or ''brushfire'' spread from the original focus. Persistent infection leads to full thickness retinal necrosis and ultimately retinal detachment in 50% of patients at 1 year after diagnosis [9,10]. CMV retinitis is most prevalent in AIDS patients occurring up to 40% [9,11,12]; however, the prevalence of the same condition in patients immunosuppressed for reasons other than AIDS is between 1 and 5% [13,14].

CMV retinitis in patients with non-Hodgkin's lymphoma is uncommon, and the incidence in this subgroup is not described in the literature although it may be underestimated due to misdiagnosis as intraocular lymphoma [7]. A comprehensive MEDLINE search through databases from 1966 to December 1995 revealed only two reports of CMV retinitis diagnosed postmortem [15,16] and two cases diagnosed by clinical fundus examination in patients with lymphoma. Both of these patients developed CMV retinitis while on treatment for their lymphoproliferative disorder. Only one of the two patients had a response to treatment with adenine arabinoside [17].

Although the incidence of infection with CMV in patients with leukemias and lymphomas is low [18,19], it may be increasing as a result of the immunosuppressive toxicity of some new chemotherapeutic agents. Both CAMPATH® 1H monoclonal antibody and fludarabine, used to treat our patient, are examples of new agents used in the treatment of recurrent or progressive low-grade lymphomas after failure of conventional chemotherapies. Both agents cause depletion of lymphocytes and have been reported to predispose patients to opportunistic infections [20,21].

CAMPATH® 1H is a humanized monoclonal antibody that destroys both normal and malignant lymphocytes by binding to the CDw52 antigen expressed in cells of almost all non-Hodgkin's lymphomas and on most normal B and T lymphocytes. Patients treated with this investigational agent in phase I/II trials developed an unacceptably high frequency of infections, which were usually viral and associated with marked lymphopenia and T-cell depletion. Four out of seven patients developed CMV infections (three developed colon mucosal biopsy conversions and one developed CMV retinitis) [20].

Fig. 1. A: Right fundus photograph from December 1994 (initial presentation of retinal disease) showing perivascular patch of retinochoroidal yellow-white discolouration with associated retinal hemorrhages inferior to right optic disc. B: Higher magnification of area of involvement shown in A. C: Fundus photograph of patient's right eye in February 1995 showing progression of retinal disease: inferior retinal detachment with associated vitreous hemorrhage obscuring the view.

Fludarabine (2-Fluoro-ara-AMP) is a purine nucleoside analog that affects dividing and nondividing cells by inhibiting with DNA synthesis and preventing DNA repair, also leading to prolonged depletion of CD4 and CD8 cells. Treatment with nucleoside analogs has been shown to contribute to a variety of opportunistic infections. There has been no reported correlation between the CD4 level and the incidence of infection [21].

The strongest association of CMV retinitis is with AIDS patients. Studies have shown that retinal infection with CMV relates to the degree of suppression of cellular immunity [22] and particularly to the level of CD4 lymphocytes [23–26]. In patients with AIDS, CMV retinitis is most often diagnosed by observing its characteristic clinical appearance of perivascular whitening or yellowing with or without haemorrhage [9,10]. In situations where the diagnosis is in question or the response to treatment inadequate, additional methods may be required in order to make a diagnosis of ocular CMV infection.

CMV serology is not used often for diagnosis of CMV target-organ disease, because this disease occurs primarily in immunosuppressed individuals who do not mount a normal immunologic response to infection. In addition, positive CMV serology occurs in 50 to 70% of normal adults [18,25].

The interest in viral detection in blood comes from the finding that CMV viraemia is associated with clinical disease. There is a strong association between CMV viraemia and CMV retinitis. In one study 50% of patients developed CMV retinitis with positive CMV blood cultures, while 9.3% developed retinitis with negative cultures [27,28]. Viral isolation in culture is considered the gold standard for CMV diagnosis [29]. The problems with culturing CMV are twofold: first, with conventional culture techniques, one requires 4 to 6 weeks to exclude an infection and, secondly, the small sample sizes available from certain clinical samples contain minute amounts of virus, which may lead to false-negative results [30].

With modern methods, the speed of detection has been enhanced by DNA hybridization probes. The problem with small sample size has been dealt with by in vitro amplification of CMV specific sequences by polymerase chain reaction (PCR) [30,31]. The entire process of viral isolation takes 1 to 2 days by PCR and nucleic acid hybridization techniques [30].

Studies in patients with AIDS suggest a correlation between CMV retinitis and isolation of PCR amplified CMV DNA in serum and/or WBC; however, no study was 100% sensitive or specific [30–33]. Although patients found to have PCR detected CMV DNA in their serum or WBC may have a high risk of CMV retinitis, patients may present with CMV viraemia with or without a diagnosis of CMV retinitis. The presence of CMV in the blood is not diagnostic of tissue destructive disease [34]. Furthermore, some patients with CMV retinitis had no detectable CMV DNA in their blood.

Intraocular fluid may be obtained by aqueous tap, vitreous tap, or vitrectomy for isolation of virus by conventional culture techniques, or by PCR techniques. Because the sample of intraocular fluids is often small, the virus may only be detectable by PCR. Fox et al. [31] found detectable CMV DNA in 9/9 vitreous, 5/9 subretinal fluid, and 3/9 aqueous specimens of patients with a clinical diagnosis of CMV retinitis. This same study found that five of six eyes from AIDS patients with no retinal disease had no detectable CMV DNA in their vitreous. Seven of eight vitreous specimens from normals were netative for CMV DNA sequences [31]. In a subsequent study, Mitchell et al. [34] demonstrated the correlation between detection of PCR amplified CMV DNA in vitreous samples with clinical retinal disease in HIV patients. In this study, 92.3% of patients with a clinical diagnosis of CMV retinitis had detectable CMV DNA in the vitreous sample. Immunocompetent controls without retinitis had no detectable CMV viral sequences in their vitreous samples in 98% of cases [34]. Although the diagnosis of CMV retinitis can be made most definitively by histologic analysis and detection of the CMV DNA or RNA in tissue by in situ hybridization [35], retinal biopsy is not often recommended because of the high risk of retinal detachment after biospy of a necrotic retina.

In summary, we have presented a case report of a patient with progressive low-grade non-Hodgkin's lymphoma who received a series of treatments for his lymphoma including some newer immunosuppressive agents (CAMPATH® 1H and fludarabine). Although the development of retinal lesions was initially thought to represent infiltration with lymphoma, subsequent appearance combined with the detection of CMV in culture of vitreous fluid and by PCR analysis helped to establish a diagnosis of CMV retinitis. In patients undergoing treatment for lymphoma, particularly with treatments that deplete T cells, intraocular lymphoma must be distinguished from opportunistic infections such as CMV retinitis. Both the ophthalmologist and the haematologist/oncologist must be aware of the rare but almost equal likelihood of CMV retinitis and intraocular lymphoma in these patients. In situations where the clinical findings are not diagnostic, rapid detection of CMV in the blood by PCR analysis may increase one's index of suspicion for CMV retinitis. When the diagnosis remains uncertain, cytologic examination, culture, and PCR analysis of intraocular fluids obtained by vitreous tap or vitrectomy may help to establish a relatively sensitive and specific diagnosis of CMV retinitis.

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